in the genesis of ischemic preconditioning in man. This finding may have implications for the mechanism of action of ACE inhibitors in ischemic heart disease.

3:00

901-5 Relation Between Perfusion, Metabolism and Functional Recovery Early After Coronary Revascularization in Patients With Hibernating Myocardium

F. Alamanni, A. Repossini, A.A. Lotto, F. Bortone, A. Parolari, E. Doria, L. Ruffini, M. Pepi, R. Accinni, P. Biglioli, O. Parodi. *Dept. of Cardiac Surgery, University of Milan, Centro Cardiologico Fondazione I. Monzino and CNR Institute of Clinical Physiology, Section of Milan, Milan, Italy*

The purpose of this study was to determine the recovery of function and its relation to regional myocardial blood flow (CBF) and metabolism soon after coronary revascularization in pts with hibernating myocardium. 15 pts (14 men, 1 women, mean age 58 ± 9 yrs) undergoing coronary artery bypass grafting (CABG) on the left anterior descending coronary artery (LAD) with hibernation in the LAD-related segments were studied. Myocardial viability in LAD territory was recognized in all by dobutamine stress echocardiography and quantitative ^{201}Tl rest-redistribution imaging. The LAD-CBF, evaluated by great cardiac vein (GCV) catheterization (thermodilution technique), the myocardial metabolic balance by artero-GCV blood samples (tested for alanine, lactate, glutamate and free fatty acids) and the regional wall motion by transesophageal echocardiography, were assessed before and 20–40 min after CABG. Regional function improved in 74% of the dyssynergies (wall motion score index from 2.7 ± 0.7 to 1.4 ± 0.7, $p < 0.001$). LAD-CBF increased in all but one pt after surgery (from 56 ± 27 to 121 ± 46 ml/min, $p < 0.001$). Myocardial substrate utilization (calculated as extraction and metabolic fluxes across the heart) in the LAD territory was indicative of lactate, glutamate and fatty acids utilization, and slight alanine production before CABG. Mean myocardial utilization of the measured substrates did not change after revascularization. At follow-up 74% of the dysfunctioning segments had function normalized or improved. In conclusion, in hibernating myocardium the aerobic metabolism is transmurally preserved, despite chronically reduced CBF and contraction. The CBF improvement, following revascularization, is associated with an immediate functional recovery in most of dysfunctioning segments, leaving unchanged the metabolic fluxes.

3:15

901-6 Transdermal Nitroglycerin Therapy Is Not Associated With Biochemical Markers of Oxidative Stress

S.D. Milone, C.R. Pace-Asciak, E.R. Azevedo, G.E. Newton, J.D. Parker. *University of Toronto, Canada*

Background: Tolerance to organic nitrates may be caused by increased free radical production. To date, no human studies have examined the impact of nitrate therapy on biochemical markers of oxidative stress. We examined the effect of nitrate therapy on: 1) plasma 8-iso-PGF2α (a stable metabolite of arachidonic acid oxidation), 2) plasma malondialdehyde (MDA; a product of lipid peroxidation), and 3) plasma Vitamin C (Vit C; via HPLC) levels.

Methods: Twenty normal males received continuous transdermal nitroglycerin (TGTN) 0.6 mg/hr or no therapy in a randomized, investigator blind, parallel design fashion. Standing HR, SBP, plasma 8-iso-PGF2α, MDA, and Vit C levels were measured at baseline, 3 hours following acute TGTN and after 1 week of sustained therapy.

Therapy was continued and the following day all subjects received 2 grams of oral Vit C or placebo in a double blind, randomized, crossover fashion. Before and 90 min after oral Vit C, measures of SBP, HR, and plasma Vit C levels were obtained.

Results: Acutely, TGTN caused a significant fall in SBP and an increase in HR. Following sustained therapy, both SBP and HR returned to baseline indicating the development of tolerance.

	Baseline	Acute TGTN	Sustained TGTN
8-iso-PGF2α (pg/mL)	267 ± 84	288 ± 111	310 ± 110
MDA (mmol/L)	4.7 ± 1.0	4.6 ± 0.9	4.2 ± 0.7
Vit C (μmol/L)	56 ± 22	60 ± 20	50 ± 25

Acute and sustained TGTN therapy was not associated with evidence of increased free radical production. The administration of Vit C failed to restore the hemodynamic effect of TGTN (SBP: 119 ± 12 vs 118 ± 9 mmHg, pre vs post Vit C) despite a significant increase in plasma Vit C levels (67 ± 48 vs 112 ± 39 μmol/L; $p < 0.01$).

Conclusion: This study demonstrates that a clinically relevant dose of TGTN therapy is not associated with biochemical evidence of oxidative stress. Consistent with this observation, the acute administration of vitamin C does not restore hemodynamic responses to TGTN. This study does not support the hypothesis that increased free radical production is a cause of tolerance to therapy with TGTN.

902 Genetic and Metabolic Risk Factors in Acute Coronary Syndromes

Wednesday, April 1, 1998, 4:00 p.m.–5:00 p.m.
Georgia World Congress Center, Room 257W

4:00

902-1 Association of a Polymorphism of the Endothelial Constitutive Nitric Oxide Synthase Gene With Myocardial Infarction in Japanese Population

S. Ichihara, Y. Yamada, T. Fujimura, M. Yokota. *Nagoya University School of Medicine, Nagoya, Japan*

Background: Nitric oxide (NO) accounts for the biological activity of endothelium-derived relaxing factor, which seems to have an important role in vasodilation and an inhibition of platelet aggregation. The important role of NO release in the regulation of basal or stimulated vascular tone suggests that an abnormal NO synthase activity could be implicated in different pathological conditions such as hypertension or atherosclerosis. Endothelial constitutive nitric oxide synthase (ecNOS) polymorphism was recently reported to be associated with coronary artery disease only in current and ex-smokers in Australia. We thus studied the association between variation in the ecNOS gene and the presence of myocardial infarction (MI) in a Japanese population.

Method: The polymorphism in intron 4 of the ecNOS gene (ecNOS4a/b) was analyzed in 455 patients with MI and 550 control subjects.

Results: The frequency of the ecNOS4a allele was significantly higher in the MI patients than in controls (odds ratio, 1.52, $p = 0.007$). When the comparison was restricted to men or women, the frequency of the ecNOS4a allele was significantly higher in the MI patients than in controls in men (odds ratio, 1.52; $p = 0.016$), but not in women. In the low-risk individuals defined by a body mass index <27 kg/m^2 and no history of hypertension, diabetes mellitus, or hypercholesterolemia, the association was especially marked (odds ratio, 2.50; $p = 0.0035$).

Conclusion: The polymorphism in intron 4 of the ecNOS gene may be an independent risk factor for MI in the Japanese population.

4:15

902-2 Increased Expression of Human Cu-Zn Superoxide Dismutase in a Transgenic Mouse Model of Ischemia/reperfusion

J.R. Teerlink, N.Y. Honbo, Y.-F.C. Lau, J.S. Karliner. *VA Medical Center/UCSF, San Francisco, CA, USA*

Background: The human (h-MnSOD) manganese-superoxide dismutase gene is readily inducible by oxidative and other stresses, but the role of the "constitutive" human Cu-Zn SOD in the cardiac response to ischemia is unclear. Our purpose was to assess the effect of ischemia/reperfusion on the expression of h-CuZnSOD in a transgenic mouse model (gift from Dr. Charles J. Epstein).

Methods: Mice were randomly selected from normal CD-1 controls, h-CuZnSOD heterozygotes (Htz) and homozygotes (Hmz) at age 6 months with a mean weight of 43 ± 3 grams. Hearts were excised, perfused on a Langendorff apparatus, and underwent 30 minutes of ischemia followed by 15 minutes of reperfusion (IschRep) or perfusion for 45 minutes (Control); experiments were performed in triplicate. SOD mRNA expression was measured on Northern blots prepared from total mRNA isolated from the mouse hearts with a h-CuZnSOD probe. Two distinct bands were measured by densitometry at approximately 0.7 and 0.9 kb in Htz and Hmz mice, the values adjusted for 18s intensity, and added as total CuZn-SOD.

Results: Baseline SOD expression was increased 5.5-fold in Hmz mice ($p = 0.06$). No significant increase in wild type mouse SOD during IschRep (control 0.3 ± 0.2 SD; IschRep 0.4 ± 0.2 units) was noted, although SOD transgene expression markedly increased in both Htz ($p < 0.01$) and Hmz ($p < 0.05$) to 3.0 ± 1.3 and 2.9 ± 0.7 units, respectively. These findings suggest minimal activation of the native mouse CuZnSOD in response to IschRep, elevated baseline h-CuZnSOD expression in the Hmz mice, and marked induction of transgene transcription in response to IschRep.

Conclusion: The expression of the constitutively expressed h-CuZn SOD gene is incompletely understood; in this transgenic model, it was readily inducible. Further study of this increased expression in response to IschRep may contribute to an increased understanding of the mechanism of myocardial salvage in ischemic states.